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Heparin Anticoagulation Monitoring in Patients Supported by Ventricular Assist Devices

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In patients supported with mechanical circulatory support (MCS), pump thrombosis is one of the most devastating complications associated with high morbidity and mortality.[1] Therefore, it is clear that these patients should receive anticoagulation (class I recommendation).[2] Despite the development of new anticoagulant agents, unfractionated heparin (UFH) continues to be the anticoagulant of choice, especially in the early postoperative phase in which close titration is required.[3] It is well known that the risk of heparin-associated bleeding increases with heparin dose, and by recent surgery, or invasive procedures.[4] Although the use of UFH is unquestioned, monitoring remains a matter of discussion. Traditionally, in percutaneous coronary intervention or cardiac surgery, the effect of UFH is monitored by the activated partial thromboplastin time (aPTT) or the activated clotting time (ACT), when higher doses of UFH are used in conjunction with extracorporeal bypass.

Although the 2013 Guidelines for MCS by the International Society for Heart and Lung Transplantation do not recommend specific measurement methods for monitoring of UFH, the authors refer to targeted aPTT levels[2]; similarly, practical clinical management instructions[5] or the American Heart Association/American College of Cardiology guidelines on patients with non-ST elevation acute coronary syndromes[6] or valvular heart disease[7] refer to target levels of aPTT. Although aPTT seems to be the standard criterion, it is known that aPTT is susceptible to physiologic and nonphysiologic factors and may underestimate or overestimate the level of anticoagulation. For this reason, plasma heparin assays—which determine the anticoagulation activity of UFH by measuring the ability of heparin-bound antithrombin to inhibit FXa—have been proposed.[8,9] Published data suggest that anti-Xa monitoring achieves therapeutic anticoagulation more rapidly, maintains the values within the goal range for a longer time, and requires fewer adjustments in dosage and repeated tests[10]; further, the aPTT is impacted more frequently by preanalytic compared with anti-Xa.[11]

Patients with ventricular assist device (VAD) have an increased bleeding and thrombotic risk.[12] An increased bleeding risk is associated with the loss of high-molecular-weight multimers of von Willebrand factor, which is caused by the high shear stress at the VAD site. Clot formation on the VAD may cause embolic stroke and/or pump malfunction. Thus, reliable monitoring of anticoagulation is mandatory to avoid overanticoagulation or underanticoagulation. As a consequence, the validity of aPTT as a measure for therapeutic UFH levels in patients supported with VADs should be questioned. In this issue, Sieg *et al*.[13] describe their retrospective experience, using an anti-XA anticoagulation protocol in a small population of adult patients receiving peripheral VAD. Patients were stratified, based on the monitoring of anticoagulation, by using aPTT or anti-Xa values. Only 43% of patients monitored with aPTT and 69% monitored with anti-Xa were within the targeted therapeutic range of UFH. Patients monitored by aPTT had increased bleeding and thrombotic event rates compared with patients monitored by anti-Xa assay. However, target anti-Xa in this protocol (0.2–0.4 IU/ml) was significantly lower than target anti-Xa usually reported in other studies (0.3–0.7 IU/ml). These data are in line with a recent prospective study by Adatya *et al*., evaluating the relationship between anti-Xa and aPTT for the monitoring of UFH in 38 patients with continuous-flow left VADs. In this study, anti-Xa and aPTT levels were discordant in 74.4% of cases, and it was suggested that anti-Xa monitoring would provide a more accurate estimate of heparin concentration.[14]

Monitoring UFH using anti-Xa assay may also be of particular advantage in pediatric patients.[3,15–17] Recently, Liveris *et al*.[18] have shown that the anti-Xa assay was better correlated with heparin dosing than the aPTT or ACT in pediatric extracorporeal membrane oxygenation, suggesting that anti-Xa assay may be a more valuable monitor of heparin administration.[18] Although still no uniform evidence-based guidelines exist on the optimal method for monitoring UFH therapy, many clinicians use anti-FXa assays preferentially in young children and in pediatric intensive care units.[19]

In conclusion, the ideal monitoring of UFH therapy remains a matter of discussion, and all methods, including aPTT, ACT, and anti-Xa, have their limitations. The new data by Sieg *et al.* further suggest that the anti-Xa assay may be more reliable than the aPTT in patients with VAD and emphasize the need for more prospective studies looking at the optimal method to monitor UHF in adult and pediatric patients with MCS. Until uniform, evidence-based guidelines are available, we fully support the conclusion of Sieg *et al*.[13] that an individualized anticoagulation protocol in the complex scenario of each patient on VAD is warranted.

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